



Evaluation of 61 Secondary Amyloidosis Patients: A Single-Center Experience from Turkey

61 Sekonder Amiloidoz Hastasının Değerlendirilmesi: Türkiyeden Tek Merkez Deneyimi

Evaluation of 61 Secondary Amyloidosis Patients

Can Huzmeli¹, Ferhan Candan¹, Gokhan Bagci², Demet Alaygut³, Binnur Bagci⁴, Esin Yildiz⁵, Ayse Seker Kockara¹, Mansur Kayatas¹

¹Department of Nephrology, Faculty of Medicine, ²Department of Medical Genetics, Faculty of Medicine,

³Department of Pediatric Nephrology, Faculty of Medicine, ⁴Department of Nutrition and Dietetics, Faculty of Health Sciences,

⁵Department of Pathology, Faculty of Medicine, Cumhuriyet University, Sivas, Turkey

Özet

Amaç: Sekonder amiloidozlu hastaların demografik, klinik ve laboratuvar özelliklerini, hastalık sebeplerini, MEFV gen mutasyonlarını ve mortalite oranlarını değerlendirmek. **Gereç ve Yöntem:** 2007-2013 arasında Cumhuriyet Üniversitesi, Tıp Fakültesi, Nefroloji kliniğine başvuran böbrek yada rektal doku biyopsisiyle sekonder amiloidoz tanısı alan toplam 61 hasta çalışmaya dahil edildi. Demografik özellikler, sekonder amiloidoz sebepleri, MEFV gen mutasyonları, ve son dönem böbrek yetmezliği (SDBY), renal transplantasyon ve mortalite oranları retrospektif olarak değerlendirildi. **Bulgular:** Etiyolojik açıdan hastaların %62.2'si (38) FMF, %9.8'i (6) bronşiyektazi ve amfizem, %4.9'u (3) tüberküloz, %3.2'si (2) FMF ve ankilozan spondilit birlikteliği, %1.6'sı (1) FMF ve romatoid artrit birlikteliği, %1.6'sı (1) FMF ve sistemik lupus eritematosus birlikteliği, %1.6'sı (1) osteomyelit, %1.6'sı (1) septik artrit, %1.6'sı (1) crohn hastalığı, %1.6'sı (1) kolon kanseri, %1.6'sı (1) bronşiyektazi ve tüberküloz birlikteliği, %1.6'sı (1) romatoid artrit ve %6.5'i (4) idiyopatik olarak değerlendirildi. Sekonder amiloidozu olan 47 hastanın 32'sinde (%68) nefrotik düzeyde proteinüri saptandı. Sekonder amiloidozlu 45 hastanın MEFV gen mutasyonları incelendi. Hastaların çoğunda M694V mutasyonu vardı. Şaşırtıcı bir şekilde, 3 vakada heterozigot E148Q mutasyonu saptadık. 12 vaka öldü ve bu hastaların 9'u SDBY idi. SDBY olan 5 vaka böbrek nakli oldu. **Tartışma:** Bu çalışmada sekonder AA amiloidoz için en yaygın sebep olarak FMF hastalığını bulduk. Daha büyük yada çok merkezli kohortlarda daha ileri çalışmalar yapılmalıdır.

Anahtar Kelimeler

AA Amiloidoz; Ailevi Akdeniz Ateşi; MEFV

Abstract

Aim: To evaluate demographic, clinical and laboratory characteristics, causes, MEFV gene mutations, and mortality rates of patients with secondary amyloidosis. **Material and Method:** 61 patients who had been diagnosed with secondary amyloidosis by renal and rectal biopsy between 2007 and 2013 in the nephrology clinic of Cumhuriyet University, Faculty of Medicine, were included in the study. Demographic characteristics, causes of secondary amyloidosis, MEFV gene mutations, end-stage renal failure (ESRF), renal transplantation, and mortality rates were examined retrospectively. **Results:** In etiological terms, Familial Mediterranean Fever (FMF) occurrence was 62.2% (38), bronchiectasis and emphysema 9.8% (6), tuberculosis 4.9% (3), coexistence of FMF and ankylosing spondylitis 3.2% (2), coexistence of FMF and rheumatoid arthritis 1.6% (1), coexistence of FMF and systemic lupus erythematosus (SLE) 1.6% (1), osteomyelitis 1.6% (1), septic arthritis 1.6% (1), Crohn's disease 1.6% (1), colon cancer 1.6% (1), coexistence of bronchiectasis and tuberculosis 1.6% (1), rheumatoid arthritis 1.6% (1), and idiopathic cases 6.5% (4). Proteinuria was determined at nephrotic level among 68% (32) of 47 patients who had secondary amyloidosis. MEFV gene mutation of 45 patients with secondary amyloidosis was assessed. Most patients had M694V gene mutation. Surprisingly, we detected heterozygous E148Q mutation in 3 cases. 12 cases died; of these, 9 had ESRF. Five cases with ESRF underwent renal transplantation. **Discussion:** We found FMF as the most common cause for secondary AA amyloidosis in this study. Further studies should be done with larger or multicenter cohorts.

Keywords

AA Amyloidosis; Familial Mediterranean Fever; MEFV

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Corresponding Author: Binnur Bağcı, Department of Nutrition and Dietetics, Faculty of Health Sciences, Cumhuriyet University, Sivas, Turkey.

T.: +90 3462192523 F.: +90 3462191261 E-Mail: binnur.koksal@hotmail.com

Introduction

Amyloidosis is a large group of diseases caused by extracellular and/or intracellular accumulation of amyloid fibril proteins due to different etiologies [1]. Accumulations are regarded as localized if seen in one organ or as systemic if seen in multiple organs. Accumulations are mostly seen in the brain, heart, kidney, liver, and digestive systems. Amyloid accumulations in organs other than the brain are generally observed as systemic. In time, the increase of amyloid accumulation causes pressure on the cells. Then atrophic changes in cells and tissue destruction occur. Also, organ dysfunctions occur due to the direct toxic effects of accumulated fibril proteins. Different clinical findings may be observed depending on the amyloid accumulation areas (localized and systemic forms) [1, 2].

Systemic amyloidosis types are mainly classified as primary (immunoglobulin light chain or AL) amyloidosis, secondary (AA) amyloidosis, and familial (hereditary) amyloidosis. To date, approximately 31 different proteins have been identified as causing amyloidosis. These proteins are structurally different from each other [3, 4].

The cause of secondary amyloidosis is an acute phase reactant known as serum amyloid A (SAA) which is the precursor protein of AA amyloidosis. The most common causes of secondary AA amyloidosis are rheumatic diseases, chronic infections, chronic arthritis, auto-inflammatory diseases, and malignancies and rheumatoid arthritis (RA) in particular [5]. The common feature of secondary amyloidosis is chronic inflammation, which is seen in all cases. SAA is synthesized in the liver through the effect of cytokines such as interleukin 1 (IL-1), (IL-6), and tumor necrosis factor (TNF)-alpha and circulates in the bloodstream as a part of high-density lipoprotein 3 fractions (HDL3) [6]. Although the main source of SAA protein is the liver, it is also synthesized in endothelial cells, macrophages, atherosclerotic smooth muscle cells, the brain, and synovium. A high SAA level alone does not cause amyloid accumulation, however it leads to macrophage activation and increased secretion of cytokines such as IL-1, IL-6, and TNF-alpha. This, in turn, is followed by amyloid accumulation. Amyloid accumulation is primarily seen in the spleen, liver and kidneys, and AA amyloidosis can lead to nephrotic syndrome and ESRD [6, 7].

Clinical findings of amyloidosis vary based on the organ involved. Proteinuria develops in renal involvement as a result of accumulation of amyloid fibrils. Proteinuria is more commonly encountered at nephrotic level. Occasionally, renal dysfunction may be observed without proteinuria. Hematuria is observed in some cases. Renal involvement eventually leads to ESRF. Systolic or diastolic dysfunction, heart failure, cardiomyopathy, various arrhythmia, and heart blocks are observed in cardiac involvement. Constrictive pericarditis and restrictive cardiomyopathy may cause accumulation in coronary arteries as well as ischemic cardiac disease. Accumulation of amyloid in the gastrointestinal system and autonomic nerves may cause complaints. In particular, macroglossia is observed [8-10].

The MEFV gene, located on chromosome 16p13.3 and encoding a protein called pyrin, is responsible for Familial Mediterranean Fever (FMF) disease. Mutations in the MEFV gene have been found in the majority of FMF patients [11-14]. The vast majority of MEFV mutations identified in FMF patients include

mutations (M680I, M694V, M694I, and V726A) clustered in exon 10 and a mutation in exon 2 (E148Q) [15]. The main concern in FMF is the development of renal amyloidosis. The severe disease phenotypes of amyloidosis were found to be associated with M694V mutation and the compound E148Q-V726A mutation [16]. Furthermore, renal amyloidosis has been reported in asymptomatic individuals who do not experience attacks of serositis (phenotype II) [17]. Colchicine is the drug of choice for the treatment of FMF and can prevent amyloidosis [11, 16]. In this study, demographic, clinical and laboratory characteristics of patients, causes of secondary amyloidosis, MEFV gene mutations, end-stage renal failure (ESRF), renal transplantation, and mortality rates were examined retrospectively.

Material and Method

Sixty-one patients diagnosed as biopsy-proven AA amyloidosis at the nephrology clinic of Cumhuriyet University, Faculty of Medicine between 2007 and 2013 were assessed retrospectively. In the process of studying patient proteinuria or renal dysfunctions in our clinic, AA amyloidosis was determined by renal and rectal biopsy. By screening patient files, we analyzed their laboratory examinations including blood urea nitrogen (BUN), serum creatinine, serum albumin, total protein, alanine aminotransferase enzyme (ALT), aspartate aminotransferase enzyme (AST), low density lipoprotein (LDL), cholesterol, high density lipoprotein (HDL), triglyceride, C-reactive protein (CRP), sedimentation, hemoglobin (Hb), hematocrit (HCT), complete urinalysis, microalbuminuria and proteinuria levels, as well as hepatomegaly and splenomegaly results through abdominal ultrasonography, and we recorded information related to their diagnoses and clinical courses. Among these patients, those diagnosed with FMF were classified as phenotype I or phenotype II. MEFV gene mutations of 45 patients with secondary amyloidosis were examined. The common mutations of MEFV gene (exon 2, 3, 5 and 10) were detected using Sanger sequencing or Strip assay methods. Patients were categorized according to their proteinuria values as < 1 gr/day, 1-3.5 gr/day and > 3.5 gr/day (nephrotic proteinuria).

Biopsy samples were primarily examined in a light microscope, then stained with Congo red and evaluated in a polarized microscope. An additional chemical process was conducted in cases who were observed to have amyloid in tissue, and cases were diagnosed with AA amyloidosis when the tissue with amyloid was exposed to potassium permanganate and amyloid dissolved from the tissue.

Statistical Analysis

All statistical analyses were performed by SPSS version 22.0 (SPSS IBM, Armonk, NY, USA). All demographic data and clinical findings were expressed as mean \pm standard deviation (and range) with a 95% confidence interval.

Results

A total of 61 patients diagnosed with secondary amyloidosis were included in the current study. Their mean age was 49.81 ± 17.93 . 41 (67.2%) of these patients were male and 20 (32.7%) were female. While the mean age of men was 47.60 ± 16.60 the mean age of women was 54.35 ± 20.07 . Table

1 shows demographic and laboratory findings of patients.

Forty-two of the patients included in the study were diagnosed with FMF. Of those, 2 cases were diagnosed with ankylosing spondylitis (AS), one case was diagnosed with RA and one case was diagnosed with (SLE) (Table 2).

MEFV mutation analysis was performed in 45 cases with secondary amyloidosis. Table 3 illustrates MEFV gene mutations of patients. Homozygous or heterozygous M694V gene mutations were determined in most of the cases. There was also coexistence of several gene mutations. R202Q mutation, rarely analyzed, was identified in 4 cases and only one case had RA in addition to FMF. We identified 3 patients with E148Q mutation. Fourteen patients had one heterozygous mutation. In mutation analysis of 9 phenotype II patients, it was found as homozygous M694V and homozygous R202Q (1), heterozygous M694V (3),

Table 1. Demographic and laboratory findings of patients.

Variable	Number	Mean±SD	Range
Age	61	49.81 ± 17.93	(17- 84)
Male	41	47.6 ± 16.6	(17-78)
Female	20	54.35 ± 20.07	(23-84)
BUN (mg/dl)	61	39.77± 34.26	(8-210)
Creatinine (mg/dl)	61	3.82 ± 3.92	(0.3-24)
Total protein (gr/dl)	61	5.57 ± 1.24	(2.6-7.8)
Albumin (gr/dl)	61	2.31 ± 1.00	(0.2-4.2)
ALT (IU/L)	61	19.36 ± 27.99	(3-225)
AST (IU/L)	61	22.75 ± 26.91	(4-219)
Hb (gr/dl)	61	11.41 ± 2.46	(5.4-16.7)
HCT (%)	61	34.48 ± 6.85	(16-48.5)
Sedimentation (mm/hour)	54	76.31 ± 35.72	(7-145)
CRP (mg/L)	56	44.42 ± 47.23	(3-220)
LDL (mg/dl)	58	120.74 ± 20.85	(36-425)
HDL (mg/dl)	53	33.3 ± 13.1	(13-83)
Cholesterol (mg/dl)	56	185.19 ± 85.4	(91-95)
Microalbuminuria (gr/day)	47	3.24 ± 3.25	(0.1-13)
Proteinuria (gr/day)	47	6.49 ± 5.02	(0.5-22.8)

BUN: Blood urea nitrogen, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, Hb: Hemoglobin, HCT: Hematocrit, CRP: C-reactive protein, LDL: Low density lipoprotein, HDL: High density lipoprotein.

Table 2. Primary diseases causing amyloidosis

Primary disease	Number (%)
Idiopathic	4 (6.5%)
FMF	38 (62.2%)
Tuberculosis	3 (4.9%)
Bronchiectasis and emphysema	6 (9.8%)
Osteomyelitis	1 (1.6%)
Septic arthritis	1 (1.6%)
Crohn's disease	1 (1.6%)
Colon cancer	1 (1.6%)
RA	1 (1.6%)
FMF and AS	2 (3.2%)
FMF and SLE	1 (1.6%)
FMF and RA	1 (1.6%)
Bronchiectasis and tuberculosis	1 (1.6%)

FMF: Familial Mediterranean Fever, AS: Ankylosing Spondylitis, SLE: Systemic Lupus Erythematosus, RA: Rheumatoid Arthritis

Table 3. MEFV Gene Mutations of Patients

Mutation	Patients (n=61) (%)
Mutation analysis not conducted	16 (26.2%)
No mutation	8 (13.1%)
Homozygous M694V	7 (11.4%)
Heterozygous M694V	5 (8.1%)
Homozygous M694V and Homozygous R202Q	1 (1.6%)
Heterozygous M694V and Heterozygous R202Q	1 (1.6%)
Heterozygous M694V and Heterozygous M680I (G/C)	3 (4.9%)
Heterozygous M694V and Heterozygous E148Q	3 (4.9%)
Heterozygous M694V and Heterozygous R761H	1 (1.6%)
Heterozygous M694V and Heterozygous V726A	1 (1.6%)
Heterozygous M694V, Heterozygous R202Q and Heterozygous V726A	1 (1.6%)
Homozygous M680I (G/C)	2 (3.2%)
Heterozygous M680I (G/C)	2 (3.2%)
Heterozygous M680I (G/C) and Heterozygous V726A	1 (1.6%)
Homozygous V726A	1 (1.6%)
Heterozygous E148Q	3 (4.9%)
Heterozygous R202Q	4 (6.5%)
Heterozygous V726A and Heterozygous F479L	1 (1.6%)

heterozygous E148Q (1), heterozygous R202Q (1), heterozygous M694V and heterozygous R761H (1), heterozygous M680I (G/C), and heterozygous V726A (1).

Of 61 amyloid patients, hemodialysis was started for a total of 35 patients (57.4%) with the diagnosis of end-stage renal failure (ESRF). 27 of them were diagnosed with FMF, 2 were diagnosed idiopathic, one was diagnosed with emphysema, 2 were diagnosed with bronchiectasis, one was diagnosed with septic arthritis, and one was diagnosed with RA. Twenty two of the FMF patients were determined to be phenotype I and 5 were determined to be phenotype II. Five of the 9 patients with phenotype II were diagnosed with ESRF.

Twelve patients were diagnosed with amyloidosis after their exitus. Seven of these exitus patients died during diagnostic evaluations, 4 patients died approximately within 6 months to one year after diagnosis, and one patient died approximately 5 years after diagnosis. Four of the exitus patients had FMF, one had FMF plus RA, 3 had idiopathic and 4 had bronchiectasis plus emphysema. Seven of the exitus patients had proteinuria at a nephrotic level, one had 1-3.5 gr/day and 1 had < 1 gr/day proteinuria. Proteinuria could not be examined for the other 3 exitus patients. Nine of the exitus patients had anemia. 9 of the 12 exitus patients were undergoing hemodialysis.

Thirty-nine patients included in the study had anemia; of these, 26 were undergoing hemodialysis. Of the 39 anemic patients, 23 had FMF (18 had phenotype I, 5 had phenotype II), one had RA plus FMF, 6 had bronchiectasis plus emphysema, 2 had tuberculosis, one had osteomyelitis, one had septic arthritis, one had colon cancer and one patient was diagnosed with RA.

Of 61 amyloidosis patients, 11 patients had hypothyroid. Seven of them were diagnosed with proteinuria at nephrotic level and 2 were diagnosed with proteinuria at non-nephrotic level. The proteinuria level of one patient could not be examined. Six of the cases with hypothyroid were undergoing hemodialysis.

CRP test was conducted for 56 patients. The results of 43 of

these patients were considered as high. Sedimentation was examined for 54 patients. The results of 49 of these patients were found to be high because of the level exceeded 25 mm/h. All patients except for 2 had low serum albumin levels (serum albumin < 4 gr/dl).

Lipid levels of patients with secondary amyloidosis were found to be generally normal; however, the HDL levels were found to be low in 73.6% (39) of patients. Twenty-eight of 38 cases with FMF had low HDL levels, 3 patients had high HDL levels, and 7 had normal HDL levels. Eight of the exitus cases had low HDL levels, 2 had normal HDL levels and one had high HDL level. Two of 10 cases whose LDL levels were above 160 mg/dl had proteinuria above 1-3.5 gr and 8 had proteinuria above 3.5 gr. All of the 8 patients whose triglyceride level was above 200 mg/dl had proteinuria at nephrotic level. Ten of 16 patients whose cholesterol level was above 200 mg/dl had proteinuria at nephrotic level and 5 had 1-3.5 gr proteinuria. The cholesterol level of one patient was not measured.

In the current study, of 61 amyloidosis patients, 56 patients had complete urine analyses, 39 of these patients had proteinuria, 16 had hematuria in addition to proteinuria, and one patient had only hematuria. Proteinuria was determined at nephrotic level among 68% (32) of 47 patients who had secondary amyloidosis. All patients except for 2 had hypoalbuminemia (serum albumin < 4 gr/dl). While hepatomegaly was found in 5 (8.3%) cases, splenomegaly was found in 9 (15%) cases.

In the current study, of 61 amyloidosis patients, 5 patients had renal transplants and also all of the cases who had renal transplants were diagnosed with FMF phenotype I. MEFV mutation results of cases who underwent transplantations were identified as: homozygous M694V (1), heterozygous M694V and heterozygous E148Q (2), heterozygous V726A and heterozygous F479L (1). Mutation analysis of one patient was not performed. Three patients had proteinuria at nephrotic level, one patient had proteinuria between 1-3 gr/day, and proteinuria of one patient was not examined. None of these patients had repeated proteinuria in renal allograft.

Discussion

Secondary amyloidosis is defined as the accumulation of amyloid on tissues and organs as a result of increasing SAA protein, which is an acute phase reactant developing in conjunction with inflammation. SAA production increases in inflammatory conditions [6]. In the current study, we evaluated demographic characteristics, etiology and mortality rates, and MEFV gene mutations of 61 secondary amyloidosis patients who were admitted to our clinic.

Although in Europe the most common cause of amyloidosis is RA, in Turkey the most common cause of amyloidosis is FMF [18]. Amyloid may develop in a period between 2 months and 14 years after FMF episodes. The period leading to ESRF after proteinuria may be 2-13 years [19]. Secondary AA amyloidosis remains the most serious manifestation of FMF. The incidence rate of secondary AA amyloidosis among FMF patients is 37% in sephardic Jews, 24% in Armenians, 8% in Ashkenazi Jews, 12% in Turks and 10% in Arabs [20, 21]. Amyloidosis development rates among FMF patients were found as 25.7% in homozygous M694V mutation, 15.4% in M694V compound het-

erozygous and 12.3% in other mutations. Amyloidosis did not develop in E148Q mutations [22].

Although heterozygous E148Q mutation was found in non-amyloid glomerular diseases [23, 24], there is still no data about whether heterozygous E148Q mutation is an amyloidosis-causing mutation. Topaloglu et al. analyzed 26 patients homozygous for E148Q, 10 compound heterozygous for E148Q, and 8 complex cases. They found that none of their patients had amyloidosis except that 2 cases with E148Q/E148Q mutation had a family history of amyloidosis and one had rapidly progressive glomerulonephritis [25]. Balci et al. investigated AA amyloidosis patients (25 phenotype II) in terms of 4 MEFV mutations (M694V, M680I (G/C), V726A and E148Q), and they observed M694V mutation as the most frequent mutation in homozygous, heterozygous and compound heterozygous states. In their study, E148Q was found as compound heterozygous with M694V mutation in 2 cases [26]. In a study conducted with 507 children with FMF in the southeast of Turkey, renal amyloidosis developed in 1.4% (n=7) of patients. Five of the patients with renal amyloidosis had homozygous M694V mutation and two of them were compound heterozygous with M694V/V726A and M694V/M680I (G/C) mutations. Two of these patients with amyloidosis were phenotype II FMF patients [27]. In a study evaluating frequency of MEFV mutations in FMF patients, it was found that 16 patients had a history of amyloidosis (3.55%). Among the cases with amyloidosis, 12 cases had M694V homozygous, one case had compound heterozygous for M694V and M680I (G/C) mutations, and one case had a complex allele for E148Q/E148Q/M694V mutations. No mutation could be detected in 2 cases with amyloidosis [28]. In Jewish renal amyloidosis patients, M694V/M694V genotype was found as the most frequent mutation. However, E148Q mutation was found as compound heterozygous state together with exon 10 mutation of MEFV gene [16, 17].

In this study, in terms of MEFV gene mutation, M694V mutation was 19.6% (homozygous 7 and heterozygous 5), M694V compound heterozygous frequency was 11.4%, M680I (G/C) mutation was 6.5% (homozygous 2 and heterozygous 2), heterozygous E148Q was 4.9% (3), and heterozygous R202Q was 6.5% (4). The number of patients with at least one exon 10 of MEFV gene mutation was 30. At least one M694V mutation was detected in 23 patients (Table 3). Our MEFV gene mutation results, especially for M694V, were in accordance with the literature. However, we identified 3 patients with E148Q mutation, which is not reported in European publications to cause amyloid accumulations. We think that this is an interesting finding, and this information can bring a new perspective to the literature about E148Q mutation and development of amyloidosis.

Because amyloid accumulation leads to renal failure, it is the most important complication in FMF patients. However, it is not related to the severity of the disease. It can also appear among FMF patients who have rare and mild attacks. Additionally, phenotype II FMF can be observed among patients with no clinical symptom experience [29]. Long-term plasma SAA level should be high for AA amyloidosis development [2]. In a study, SAA levels were determined to be high in 40% of clinical phenotype III cases [30]. Clinical findings of mild FMF were observed in heterozygous persons. Acute phase responses were

higher among heterozygous persons than in the healthy control group [30, 31]. Similarly, amyloid accumulation was determined in non-compound heterozygous cases in our study. In addition, 9 cases with FMF phenotype II were determined. During diagnosis, ESRF was observed in 5 of these patients.

The frequency of amyloidosis in autopsies in Western countries has varied between 0.50% and 0.86%. According to the reported series in England and USA, more than half of the cases have juvenile and adult RA. Ankylosing spondylitis is the second most frequent cause with rates up to 12%. It is followed by psoriatic arthritis with the rate of 4-5% [32-34]. AA amyloidosis is a rare complication of RA. However, there have been significant differences among publications. AA amyloid prevalence in RA ranges between 4% and 26% in literature [35]. AA amyloid was higher (14-61%) in RA patients in the post-mortem period [36]. Similarly, one patient had RA and one patient had coexistence of FMF and RA in our study. The most common cause of secondary amyloidosis in Turkey is reported as FMF [18]. Furthermore, the RA-related secondary amyloidosis frequency has been found to be low. In 2 studies conducted in ankylosing spondylitis patients who lived in Europe, amyloidosis rates were 7% and 9% respectively, as determined by rectal and fat biopsy screenings [37, 38]. In the current study, we found 2 (3.2%) cases who had coexistence of ankylosing spondylitis and FMF.

In the current study, there was 3 occurrences of tuberculosis, one of osteomyelitis, one of septic arthritis, and one coexistence of bronchiectasis and tuberculosis among patients with infectious diseases. As in other studies, the most common cause of infectious diseases was found to be tuberculosis in our study. Tuberculosis is the most commonly seen of the chronic infections that cause secondary AA amyloidosis; it is followed by osteomyelitis, chronic bronchitis, chronic mucocutaneous ulcer, leprosy, Q fever, and subacute bacterial endocarditis [1].

In a study that included 287 secondary amyloidosis patients from 11 centers in Turkey, the etiological causes were determined as FMF in 64% of patients, tuberculosis in 10%, bronchiectasis and chronic obstructive pulmonary disease in 6%, RA in 4%, spondyloarthritis in 3%, chronic osteomyelitis in 2%, other causes in 4%, and idiopathic in 7%. While hepatomegaly was 17%, splenomegaly was 11% [18]. In another study that evaluated 59 renal amyloidosis cases, 18 patients (30.5%) were found to have FMF, 12 (20.3%) had pulmonary tuberculosis, 8 (13.5%) had chronic osteomyelitis, 9 (15.2%) had bronchiectasis, 4 (11.8%) had RA, one (1.6%) had Castleman disease, and 7 (11.8%) were idiopathic [39]. In a study including 40 amyloidosis patients between 2003 and 2009 in Egypt, secondary amyloidosis was determined in 32 of patients and primary amyloidosis was determined in 8 patients. 30% of secondary amyloidosis cases (12) were FMF, 20% (8) were pulmonary tuberculosis, 10% (4) were chronic osteomyelitis, 10% (4) were bronchiectasis, 7% (3) were RA, and 2% (1) were rheumatic heart disease [40]. In another study, the most common cause of secondary amyloidosis was RA, which was followed by recurrent pulmonary infections at the rate of 11%, Crohn's disease at 5%, ankylosing spondylitis at 5%, tuberculosis at 3%, osteomyelitis at 2%, FMF at 2%, Hodgkin's lymphoma at 2%, and idiopathic cases at 5% [41].

In a multicenter study conducted in Australia and New Zealand,

58,422 patients who underwent renal replacement treatments between 1963 and 2010 were examined; 490 (0.8%) of these patients had problems related to secondary amyloidosis. Survival rates of patients with dialysis-induced secondary amyloidosis were found to be worse and renal allograft survival and renal allograft recurrence were worse compared to those related to other diseases. A significant number of deaths were observed due to amyloidosis complications in amyloidosis-related ESRF. When amyloidosis-related ESRF and ESRF related to other causes were compared, cardiac death rates were 37% and 41%, respectively. However, death from heart failure was more common in the amyloidosis-related group (8.6% vs. 2.2%). No difference was found between the 2 groups in the 10-year follow-up in terms of dialysis interruption, infection, cancer, and other causes of death [42]. One, 2 and 6-year survival rates in the retrospective analysis of 48 ESRF patients with systemic amyloidosis (72%, 62%, and 44% respectively) were significantly lower compared to non-diabetic controls (95%, 91%, and 81%) [43]. In our study, 35 patients were diagnosed with ESRF and transferred to hemodialysis. In a retrospective study performed with 23 amyloidosis patients who underwent renal transplant operations, 10-year patient and graft survival rates were found as 66% and 68% respectively, and no significant difference was found between them and 47 non-amyloidosis control patients (57% and 87%). Recurrent amyloid rates in renal allograft were 4.3% [44]. In a study comparing 45 amyloidosis transplant receivers and 45 control patients, 3-year patient survival rates were 51%, compared to 79% in the control group. Graft survival was 45% as opposed to 38% in the control group. Recurrent amyloidosis rate in renal allograft was 9% [45]. In this study, 5 patients underwent renal transplant. No amyloid developed in renal allograft cases.

It is important to form a clinical picture of FMF in Turkey, especially in the province of Sivas where FMF is most frequently observed [12-14]. Screening of individuals who have FMF in their family histories and evaluating the treatments of phenotype III cases that have mutations but do not show clinical symptoms are prominent issues to be examined. Although studies have been conducted on phenotype II cases, when we consider that secondary amyloidosis can also develop in non-compound heterozygous mutations, it should be clarified through future studies whether phenotype III cases should be detected in early stages and treated through the evaluation of acute phase reactants.

As stated in other studies conducted in Turkey, we found FMF to be the most common cause of secondary amyloidosis. Surprisingly, we detected heterozygous E148Q mutation in 3 cases with amyloidosis. This finding can bring a new perspective to the literature about E148Q mutation and the development of amyloidosis. We suggest that further studies should be done with larger or multicenter cohorts.

Compliance with Ethical Standards

Ethical approval: The Ethics Committee of Cumhuriyet University, Faculty of Medicine approved the present study. The study was conducted in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Competing interests

The authors declare that they have no competing interests.

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